REMARKS

Claims 2-9 are pending in this application. Claim 5 has been amended.

Rejection under 35 U.S.C., § 112, first paragraph

Written Description

The Office rejected claims 2-9 as failing to comply with the written description requirement of 35 U.S.C. §112, because the amino acid and nucleotide sequences of the protein to be modified are not disclosed. *Advisory Action*, page 2. The Office argues that the claims are directed to a large genus of human antithrombin variants without describing the structure of a representative species. *Id.* However, significant evidence is available demonstrating that the inventor had possession of the claimed invention as of the filing date.

Information which is well known in the art need not be described in detail in the specification; there is no need to disclose what is already known. MPEP §2163. The amino acid sequence of human antithrombin III is well known in the art. The Applicant himself published the amino acid sequence in 1994 in a globally-distributed journal, The Journal of Biochemistry. *See* F. Tokunaga, T. Koide et al., "Amino Acid Sequence of Porcine Antithrombin III," *J. Biochem.* 116: 1164-1170, 1167 (1994). Furthermore, the specification makes reference to Japanese Patent No. 262598/1990, corresponding to EP 0384122, which discloses the complete amino acid sequence of natural human antithrombin III. *See Specification*, page 4; European Patent No. 0384122, Table 1 (issued January 19, 1990). A copy of EP 0384122 was provided with the Information Disclosure Statement filed on December 21, 2001.

Moreover, "(t)he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." *In re Wertheim,* 541 F.2d 257, 262 191 USPQ 90 (CCPA 1976). Given that the present specification is read in light of the inventor's prior publication of the natural human antithrombin III sequence, there can be no doubt that the inventor had possession of the invention as of the application's filing date.

Additionally, the specification also discloses a description of the sequence to be modified by providing 12 specific reference points. Specifically, the specification identifies the antithrombin III to be modified by indicating that the amino acid sequence is a 432 human antithrombin III sequence having cysteine residues in positions 8, 21, 95, 128, 247, and 430, asparagnine residues in positions 96, 135, 155, and 192, an arginine residue in position 393 and a serine residue in position 394. *See Specification,* page 2. The sequence disclosed in both the Tokunaga reference and in the '713 patent matches at all 12 reference points; for example, all three sources show a "c" in position 8, representing cysteine. A skilled artisan would be able to check the amino acid sequence known in the art against these reference points.

Finally, the Office provides an example of the adequacy of this written description in making the 35 U.S.C. §103 rejection. *See Advisory Action*, pages 3-4. When *Huntington II* discloses a substitution at position 380 of the antithrombin III amino acid sequence, the Office believes it to be position 380 of the identical antithrombin III sequence disclosed in the present application. Were there ambiguity about the sequence to be modified, the argument that *Huntington II 's* disclosure

rendered the claimed antithrombin variants obvious would be immediately foreclosed.

Because the amino acid sequence of human antithrombin III is well known in the art, was previously published by Applicant himself, and is described by multiple reference points within the specification, ensuring that Applicant was in possession of the claimed invention, Applicant respectfully requests that the §112, first paragraph rejection be withdrawn.

Rejection under 35 U.S.C. §103

The Office reiterated its rejection of claims 5 and 9 under 35 U.S.C. §103 as obvious in light of J.A. Huntington *et.al.*, *Biochemistry*, 1998, 37: 3272-3277 *(Huntington II),* J.A. Huntington *et.al., Biochemistry*, 1996, 35: 8495-8503 (*Huntington I)*, and common knowledge in molecular biology. Applicant respectfully requests that the Office reconsider this rejection in light of the current amendments to claim 5.

The Office has stated that antithrombin variants made by substituting Ala, Gly or Thr in position 380 are not obvious because they are less bulky than the native serine. *Advisory Action*, page 6. The Office, however, argues that *Huntington II* renders substituting an amino acid bulkier than serine in position 380 obvious. *Advisory Action*, page 5. Applicant respectfully disagrees, because *Huntington II* does not teach any limitations of the tryptophan and modified-cysteine variants that would motivate a skilled artisan to look beyond these substitutions in creating a heparin-independent antithrombin variant. Implicit in the Office's argument, however, is the suggestion that substitution of amino acids less bulky than serine

would not be obvious. Accordingly, to expedite prosecution, Applicant has amended claim 5 as discussed below.

Huntington I discloses a tryptophan antithrombin variant, while *Huntington II* discloses a cysteine variant. However, *Huntington II's* cysteine variant is actually constructed using a cysteine derivative that has been made more bulky through the addition of a flourescein group. *See Huntington II*, abstract. *Huntington II*, therefore, implies that native cysteine is **not** bulky enough to create a heparin-independent antithrombin III variant. As a result, the only positive marker Huntington provides as to adequate bulkiness is the tryptophan variant of his 1996 paper. Accordingly, in light of the Examiner's statements, variants constructed using amino acids less bulky than tryptophan are not obvious in light of the Huntington references.

In determining bulkiness, Applicant has referenced the maximum width of amino acid side chains as a proxy for bulkiness, thereby providing an objective scale. *See* Niwa and Ogino, "Multiple Regression Analysis of the Beta-Sheet Propensity of Amino Acids," *J of Mol. Struct.* (1996)155-160, at 157 (Exhibit 1). Tryptophan has a *B*5 value of 5.90. *Id.* Applicant has amended claim 5 to delete Arg and Tyr, which have *B*5 values greater than or equal to 5.90. Because *Huntington II* specifically identifies bulkiness as a functional aspect of the substitute amino acids used to create heparin independent antithrombins, a person skilled in the art would not have a reasonable expectation of success in substituting an amino acid less bulky than tryptophan. Accordingly, Applicant respectfully requests that the Office withdraw its rejection of claims 5 and 9 in light of this amendment.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: August 9, 2004

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